REMARKS

Upon entry of the accompanying amendment, Claims 1-5, 8, 9, and 12 are all the claims pending in the application. Claim 12 is withdrawn as directed to non-elected invention. Claim 1 has been amended to incorporate the feature of claims 6, 7, 10, and 11, and claims 6, 7, 10, and 11 have been canceled, accordingly. Claim 2 has been amended to more clearly state the invention.

Therefore, no new matter has been introduced. Entry of the amendment and reconsideration of the application are respectfully requested.

Applicants thank the Examiner for acknowledging and considering amendments and arguments filed August 22, 2007. In particular, Applicants extend their appreciation that the Examiner has withdrawn previous rejections under 35 U.S.C. § 102.

Applicants further thank the Examiner for acknowledging and accepting the drawings filed August 22, 2007.

Claim Rejection under 35 U.S.C. § 112

The Office states that claims 1-11 remain rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants note that the recitation "a C-terminal residue" (rather than *the* C-terminal residue) in claim 1 and the recitation "bonded to the respective N-terminal of the polypeptide" were pointed out.

In this connection, the Examiner's kind attention is invited to the fact that the expressions "a C-terminal residue" and "the respective N-terminal" in claims 1 and 2 have been replaced, respectively, with --**the** C-terminal residue-- and --the respective N-terminal **residue**-- which refer to a single particular residue.

Accordingly, it is believed that the rejection is rendered moot by the amendments and its withdrawal is respectfully requested.

Rejection Under 35 U.S.C. § 103

The Office has rejected claims 1-11 under 35 U.S.C. 103(a) as allegedly being unpatentable over Braxton (US 5,766,897, cited previously) ("Braxton") and Kay *et al.* (US 2002/0077294, cited previously) ("Kay").

Braxton is relied upon to teach a PEG-polypeptide dimeric complex (column 13 line 56) of the general formula R1-S-PEG-S-R2 where RI and R2 may represent the same or different proteins. It is asserted that Braxton teaches that human growth hormone (hGH) (Table IA and column 12 line 1) is a polypeptide that can be a part of the complex (compare claim 4 limitation) which would result in hGH-firstPEGhGH; and that PEG can be attached at particular residues (column 12 line 49). It is further asserted that Braxton teach that the residue could be naturally present in the protein or could be introduced by site-directed mutagenesis (column 13 line 64-66); that the PEG linker/moiety (i.e. first PEG) may be in the range of 0.2-20 kDa (column 12 line 50); and that a lysine residue is typically reacted with PEG (column 2 line 12).

The Office notes that Braxton does not expressly teach further pegylation of the PEG dimer with PEG of a different molecular weight, nor expressly teach the PEG groups such as those recited in claim 5 and 8 of the current invention.

Kay is relied upon to fill the gap. The Office asserts that Kay teaches polypeptide derivatives in which a protein is linked to a nonproteinaceous moiety (e.g. a polymer) in order to modify properties (section 0146); and teaches PEG as an example of the polymer (section 0148) and its modification at the amino terminus of the protein (section 0157). The Office further asserts that Kay teaches protein dimers via PEG crosslinkers (section 0161); and the polymer (i.e. PEG) having a molecular weight of 2-100 kDa (section 0149)

It appears to Applicants that the Office takes a position that one would be motivated by Braxton to obtain a polypeptide-first PEG-polypeptide dimeric protein (i.e. hGH-firstPEG-hGH) since Braxton teaches such a protein; and the pegylation of the dimer (hGH-PEG-hGH) would be desirable and result in secondPEG-hGH-firstPEG-hGH-secondPEG where the molecular weight of first PEG is 0.2-20 kDa and the molecular weight of the second PEG is 2-100 kDa.

In this regard, Applicants note that, for purposes of examination, the Office has interpreted broadly the location of the first PEG linkage to include any N-terminal region residue, and reach the conclusion that the combination of Baxton and Kay teaches or each and every element of claim 1 of the present application.

Applicants respectfully disagree for the following reasons.

First, the Examiner's kind attention is invited to the fact that **claim 1 has been amended to limit the respective molecular weight ranges of the first and second PEG molecules** by

incorporating therein the disclosures of claims 7 and 11, and lines 13-14 and 19-21, page 4 of the specification as originally filed, with the cancellation of claims 6, 7, 10 and 11.

Therefore, **the subject invention** defined in currently presented claims 1 to 5, 8 and 9, is directed to a [second PEG]-[polypeptide]-[first PEG]-[polypeptide]-[second PEG] complex, **the first and second PEG molecules having molecular weights ranging from 2 to 20 kDa and from 20 to 40 kDa, respectively**, and the molecular weight of the second PEG molecule being larger than that of the first PEG molecule.

In other words, the currently claimed PEG-polypeptide homodimer complex has a structure in which the specified parts of two molecules of a polypeptide are connected via the first PEG molecule having a small molecular weight of 2 to 20 kDa, to **minimize the decrease in the biological activity thereof**, and wherein the respective polypeptide is modified with the second PEG molecule having a larger molecular weight of 20 to 40 kDa, to **increase the *in vivo* stability of the polypeptides to prolong *in vivo* activity thereof** (*see* lines 14-21, page 2; and lines 13-14 and 19-21, page 4 of the present specification). Such beneficial effects of the subject invention (i.e., the currently claimed PEG-polypeptide homodimer complex has a prolonged half-life, while maintaining the activity of the physiologically active polypeptide) are fully supported by the results of Test Examples 5 and 6 (Table 4 and Fig. 3).

By contrary, as opposed to the Office's assertion, **both of Braxton and Kay each disclose only a single range of the molecular weight of the PEG molecule, i.e., "0.2 to 20 kDa" and "2 to 100 kDa," respectively**, and, thus, they are silent on the use of the above-mentioned two PEG molecules having the molecular weight different from each other and the

effects flowing therefrom, especially the effect in connection with the durability of the polypeptide activity. They also fail to provide any suggestion or motivation to modify the PEG-polypeptide complex to reach the currently claimed invention, with reasonable expectation of success.

As described above, it is believed that **each and every element of the currently claimed invention, as discussed above, as well as the aforementioned benefits arising therefrom are not taught, suggested or disclosed by the cited references, even if they are combined**.

Therefore, the subject invention defined in currently presented claims 1 to 5, 8 and 9 is clearly patentable over Braxton and Kay, in combination, and it is respectfully requested that the rejections of claims 1 to 5, 8, and 9 under 35 U.S.C. 103 be withdrawn.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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Date: January 29, 2008